



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 9/16, 9/50, 31/415		A1	(11) International Publication Number: WO 94/05263
			(43) International Publication Date: 17 March 1994 (17.03.94)
(21) International Application Number: PCT/EP93/02327 (22) International Filing Date: 27 August 1993 (27.08.93) (30) Priority data: 92202664.6 3 September 1992 (03.09.92) EP (34) Countries for which the regional or international application was filed: DE et al.		(74) Agent: QUAGHEBEUR, Luc; Janssen Pharmaceutica N.V., Patent Department, Turnhoutseweg 30, B-2340 Beerse (BE). (81) Designated States: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except US): JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE). (72) Inventors; and (75) Inventors/Applicants (for US only) : GILIS, Paul, Marie, Victor [BE/BE]; Schransdriesstraat 14, B-2340 Beerse (BE). DE CONDE, Valentin, Florent, Victor [BE/BE]; Kolonie 57, B-3920 Lommel (BE). VANDECRUYS, Roger, Petrus, Gerebern [BE/BE]; Langstraat 108, B-2260 Westerlo (BE).		Published With international search report.	
(54) Title: BEADS HAVING A CORE COATED WITH AN ANTIFUNGAL AND A POLYMER			
(57) Abstract			
<p>The present invention is concerned with beads comprising a 25-30 mesh core, a coating film of a hydrophilic polymer and an antifungal agent, and a seal coating layer; pharmaceutical dosage forms comprising said beads and a method of preparing said beads.</p>			
BEST AVAILABLE COPY			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BG	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LJ	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LU	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TC	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FI	Finland				

BEADS HAVING A CORE COATED WITH AN
ANTIFUNGAL AND A POLYMER

5

10 The present invention is concerned with a novel composition of antifungal agents which have low solubility in aqueous media, a process for preparing said composition and pharmaceutical dosage forms for oral administration comprising said novel composition.

15 The development of efficacious pharmaceutical compositions of azole antifungals such as for example, itraconazole and saperconazole, is hampered considerably by the fact that said antifungals are only very sparingly soluble in water. The solubility and bioavailability of said compounds can be increased by complexation with cyclodextrins or derivatives thereof as described in WO 85/02767 and US-4, 764, 604. Yet, there still exists an important demand for formulations of antifungal agents with good bioavailability for oral administration.

20

Itraconazole or (+)-cis-4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one, is a broadspectrum antifungal compound developed for oral, parenteral and topical use and is disclosed in US-4,267,179. Its difluoro analog, saperconazole or (+)-cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-2,4-dihydro-2-(1-methoxypropyl)-3H-1,2,4-triazol-3-one, has improved activity against Aspergillus spp. and is disclosed in US-4,916,134.

25

30 Unexpectedly, it has now been found that the incorporation of poorly soluble antifungal agents in hydrophilic polymers and applying this mixture as a coat film over many small beads, yields a composition with good bioavailability which can conveniently be manufactured and which is suitable for preparing pharmaceutical dosage forms for oral administration.

35

In particular the present invention is concerned with beads which comprise (a) a central, rounded or spherical core, (b) a coating film of a hydrophilic polymer and an antifungal

agent and (c) a seal-coating polymer layer, characterized in that the core has a diameter of about 600 to about 700 μm (25-30 mesh).

5 Beads obtainable from 25-30 mesh cores comprise approximately, by weight based on the total weight of the bead : (a) 20 to 60 percent core material; (b) 25 to 50 percent hydrophilic polymer; (c) 10 to 25 percent antifungal agent; and (d) 2 to 5 percent seal coating polymer.

10 The particular size of the cores is of considerable importance. On the one hand, if the cores are too large, there is less surface area available for applying the drug coating layer, which results in thicker coating layers. This raises problems in the manufacturing process as an intensive drying step is needed to reduce residual solvent levels in the coating layer. The intense drying conditions may adversely effect drug dissolution from the beads and should therefore be controlled extremely well during the manufacturing
15 process. On the other hand, small cores have a larger total surface available for coating resulting in thinner coating layers. Consequently a far less intensive drying step can be used to decrease residual solvents levels. Cores which are too small, e.g. 30-35 mesh cores, however, have the disadvantage of showing considerable tendency to agglomerate during the coating process. Therefore, 25-30 mesh cores represent the
20 optimum size where neither agglomeration nor an intensive drying step unduly constraint the manufacturing process.

Materials suitable for use as cores in the beads according to the present invention are manifold, provided that said materials are pharmaceutically acceptable and have
25 appropriate dimensions (about 25-30 mesh) and firmness. Examples of such materials are polymers e.g. plastic resins; inorganic substances, e.g. silica, glass, hydroxyapatite, salts (sodium or potassium chloride, calcium or magnesium carbonate) and the like; organic substances, e.g. activated carbon, acids (citric, fumaric, tartaric, ascorbic and the like acids), and saccharides and derivatives thereof. Particularly suitable materials
30 are saccharides such as sugars, oligosaccharides, polysaccharides and their derivatives, for example, glucose, rhamnose, galactose, lactose, sucrose, mannitol, sorbitol, dextrin, maltodextrin, cellulose, sodium carboxymethyl cellulose, starches (maize, rice, potato, wheat, tapioca) and the like saccharides.

35 A particularly preferred material suitable for use as cores in the beads according to the present invention is represented by 25-30 mesh sugar spheres (NF XVII, p 1989) which

consist of 67.5% - 91.5% (w/w) sucrose, the remainder being starch and possibly also dextrines, and which are pharmaceutically inert or neutral.

- 5 The drug coating layer preferably comprises a hydrophilic polymer such as hydroxypropyl methylcellulose (Methocel®, Pharmacoat®), methacrylate (Eudragit E®), hydroxypropylcellulose (Klucel®), or a polyvidone. Preferably hydroxypropyl methylcellulose with low viscosity, i.e. about 5 mPa.s, is used, e.g. hydroxypropyl methylcellulose 2910 5 mPa.s. Preferred antifungal agents for use as drugs in said drug coating layer are lipophilic azole antifungals, in particular itraconazole and
- 10 saperconazole. Optimum dissolution results are obtained when using a drug : polymer ratio (w/w) of about 1:1 to about 1:2, preferably about 1:1.5. In the drug coating layer, the drug substance is present in a solid dispersion or solution state as can be confirmed by differential scanning calorimetry.
- 15 A seal coating polymer layer is applied to the drug coated cores to prevent sticking of the beads which would have the undesirable effect of a concomitant decrease of the dissolution rate and of the bioavailability. Preferably a thin layer of polyethylene glycol (PEG), in particular polyethylene glycol 20000 is used as a seal coating polymer layer.
- 20 The preferred beads comprise approximately : (a) 26 to 38 percent sugar; (b) 32 to 33 percent hydroxypropyl methylcellulose 2910 5 mPa.s; (c) 21 to 22 percent itraconazole or saperconazole; and (d) 3 to 4 percent polyethylene glycol 20000.

- In addition, the beads according to the present invention may further contain various
- 25 additives such as thickening agents, lubricants, surfactants, preservatives, complexing and chelating agents, electrolytes or other active ingredients, e.g. antiinflammatory agents, antibacterials, disinfectants or vitamins.

- The beads according to the present invention can conveniently be formulated into
- 30 various pharmaceutical dosage forms. Suitable dosage forms comprise an effective antifungal amount of beads as described hereinbefore. Preferably, the beads are filled in hard-gelatin capsules such that an amount of, for example, 50 or 100 mg of the active ingredient is available per dosage form. For example, hard-gelatin capsules of size 0 are suitable for formulating beads comprising 20 to 25 percent by weight itraconazole or
- 35 saperconazole, equivalent to about 100 mg active ingredient.

- The beads according to the present invention are conveniently prepared in the following manner. A drug coating solution is prepared by dissolving into a suitable solvent system appropriate amounts of an antifungal agent and a hydrophilic polymer. A suitable solvent system comprises a mixture of methylenechloride and an alcohol, preferably ethanol which may be denatured, for example, with butanone. Said mixture should comprise at least 50% by weight of methylenechloride acting as a solvent for the drug substance. As hydroxypropyl methylcellulose does not dissolve completely in methylenechloride, at least 10% alcohol has to be added. Preferably a relatively low ratio of methylenechloride/alcohol is used in the coating solution, e.g. a ratio
- 5 methylenechloride / ethanol ranging from 75/25 (w/w) to 55/45 (w/w), in particular about 60/40 (w/w). The amounts of solids, i.e. antifungal agent and hydrophilic polymer, in the drug coating solution may range from 7 to 10% (w/w) and preferably is about 8%.
- 10
- 15 The drug coating process of the 25-30 mesh cores is conveniently conducted in a fluidized bed granulator (e.g. Glatt type WSG-30) equipped with a Wurster bottom spray insert (e.g. an 18 inch Wurster insert). Obviously the process parameters will depend on the equipment used.
- 20 The spraying rate should be regulated carefully. Too low a spraying rate can cause some spray drying of the drug coating solution and result in a loss of product. Too high a spraying rate will cause overwetting with subsequent agglomeration. Agglomeration being the most serious problem, lower spraying rates may be used initially, to be increased as the coating process proceeds and the beads grow larger.
- 25
- 30 The atomizing air pressure with which the drug coating solution is applied also influences the coating performance. Low atomizing air pressure results in the formation of larger droplets and an increased tendency toward agglomeration. High atomizing air pressure could conceivably carry the risk of spray drying of the drug solution, but this was found not to be a problem. Consequently, atomizing air pressure may be set at nearly maximum levels.
- 35
- Fluidizing air volume can be monitored by operating the exhaust air-valve of the apparatus and should be set in such a manner that optimum bead circulation is obtained. Too low an air volume will cause insufficient fluidization of the beads; too high an air volume will interfere with the bead circulation due to countercurrent air streams developing in the apparatus. In the present process optimum conditions were obtained

by opening the exhaust air valve to about 50% of its maximum and gradually increasing the opening thereof to about 60% of the maximum as the coating process proceeded.

5 The coating process is advantageously conducted by employing an inlet-air temperature ranging from about 50°C to about 55°C. Higher temperatures may speed up the process but have the disadvantage that solvent evaporation is so rapid that the coating liquid is not spread uniformly on the surface of the beads resulting in the formation of a drug coating layer with high porosity. As the bulk volume of the coated beads increases, drug dissolution may decrease significantly to unacceptable levels. Obviously, the
10 optimum process temperature will further depend on the equipment used, the nature of the core and the antifungal agent, the batch volume, the solvent and the spraying rate.

Parameter settings for optimum coating results are described in more detail in the example hereinafter. Running the coating process under those conditions was found to
15 yield very reproducible results.

In order to decrease residual solvent levels in the drug coating layer, the drug coated cores can conveniently be dried in any suitable drying apparatus. Good results may be obtained using a vacuum tumbler-drier operated at a temperature from about 60°C to
20 about 90°C, preferably about 80°C, a reduced pressure ranging from about 150-400 mbar (15-40 kPa), preferably 200-300 mbar (20-30 kPa), for at least 24 hours, preferably about 36 hours. The vacuum tumbler-drier is conveniently rotated at its minimum speed, e.g. 2 to 3 rpm. After drying, the drug coated cores may be sieved.

25 The seal coating polymer layer is applied to the drug coated cores in the fluidized bed granulator with Wurster bottom spray insert. The seal coating solution can be prepared by dissolving an appropriate amount of a seal coating polymer into a suitable solvent system. Such a system, is, e.g. a mixture of methylene chloride and an alcohol, preferably ethanol which may be denatured with, for example, butanone. The ratio of
30 methylene chloride/alcohol used may be similar to the ratio used in the drug coating process and thus can range from about 75/25 (w/w) to about 55/45 (w/w) and in particular is about 60/40 (w/w). The amount of seal coating polymer in the seal coating spraying solution may range from 7 to 12% (w/w) and preferably is about 10%. The seal coating spraying solution is advantageously stirred during the seal coating process.
35 The parameter setting for conducting this last step is essentially similar to that used in the drug coating process. Appropriate conditions are described in more detail in the example hereinafter.

A further drying step may be required after applying the seal coating polymer layer. Excess solvents could easily be removed while operating the apparatus at the parameter settings used for about 5 to 15 minutes after the spraying had been completed.

5

Both the drug coating process and the seal coating process are preferably conducted under an inert atmosphere of e.g. nitrogen. The coating equipment should preferably be grounded and provided with an appropriate solvent recovery system containing an efficient condensing system.

10

The drug coated and seal coated beads may be filled in hard-gelatin capsules using standard automatic capsule filling machines. Suitable earthing and de-ionisation equipment can advantageously prevent development of electrostatic charges.

15 Capsule filling speed may influence weight distribution and should be monitored. Good results are obtained when operating the equipment at about 75% to 85% of the maximum speed and in many cases when operating at full speed.

Using the process parameters described above, a convenient, reproducible
20 manufacturing method for preparing beads comprising a 25-30 mesh core, a drug coat layer of an antifungal agent and a hydrophilic polymer and a thin seal-coating polymer layer can be obtained. Pharmacokinetic studies showed that the thus obtained beads have excellent dissolution and bioavailability properties.

25 Example

a) Itraconazole spraying solution

An inox vessel was charged with methylene chloride (375 kg) and denatured ethanol (250 kg) through a filter (5 μ). Itraconazole (21.74 kg) and hydroxypropyl methylcellulose 2910 5 mPa.s (32.61 kg) was added while stirring. Stirring was
30 continued until complete dissolution was obtained (A suitable saperconazole spraying solution was obtained using an identical procedure).

b) Seal-coating spraying solution

An inox vessel was charged with methylene chloride (21.13 kg) and polyethylene glycol 20000 (Macrogol 20000) (3.913 kg) while stirring. Denatured ethanol
35 (14.09 kg) was added and the solution was stirred until homogeneous.

c) Drug coating process

5 A fluidized-bed granulator (Glatt, type WSG 30) equipped with a 18 inch Wurster (bottom spray) insert was loaded with 25-30 mesh (600-700 μm) sugar spheres (41.74 kg). The spheres were warmed with dry air of 50°- 55°C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 50% of its maximum in the beginning, increasing up to 60% at the end of the spraying process. The previously prepared itraconazole spraying solution was then sprayed on the spheres moving in the apparatus. The solution was sprayed at an initial delivery rate of about 600 to 700 $\text{g}\cdot\text{min}^{-1}$ at an atomizing air pressure of about 3.5 kg/cm^2 (0.343 MPa). After delivery of about 30% of the spraying solution, the delivery rate was increased to 700-800 g/min .

10 When the spraying process was completed, the coated spheres were dried by further supplying dry air of 50°- 55°C for about 10 minutes. The coated spheres were then allowed to cool in the apparatus by supplying dry air of 20-25°C for about 10 to 20 minutes. The apparatus was emptied and the coated spheres were collected.

d) In-between drying

20 In order to minimize residual solvent levels the coated spheres were then subjected to a drying step. The coated spheres were introduced in a vacuum tumbler-drier and dried for at least 24 hours, preferably about 36 hours, at a temperature of about 80°C at a pressure of about 200-300 mbar (20-30 kPa). The tumbler-drier was operated at its minimal rotation speed (2 to 3 rpm). The dried coated spheres were sieved with a sieve (Sweco S24C; sieve mesh width 1.14mm).

25 e) Seal-coating process

The dried coated spheres were introduced again in the fluidized-bed granulator equipped with the Wurster insert and warmed with dry air of 50 - 55°C. The previously prepared seal-coating spraying solution was then sprayed on the coated spheres moving in the apparatus. The solution was sprayed at an delivery rate of about 400 to 500 $\text{g}\cdot\text{min}^{-1}$, at an atomizing air pressure of about 2.5 bar (0.25 MPa). When the spraying process was completed, the beads were dried by further supplying dry air of 50 - 55 °C for 10 min. The coated spheres were then allowed to cool in the apparatus by supplying dry air of 20°-25°C for about 5 to 15 minutes. The beads were removed from the apparatus and stored in suitable containers.

35

f) Capsule filling

The drug coated beads were filled into hard-gelatin capsules (size 0) using standard automatic capsule filling machines (e.g. Model GFK-1500, Höfflinger and Karg, Germany). In order to obtain capsules with good weight distribution, capsule filling speed was reduced to about 75-85% of the maximum speed. Each capsule received approximately 460 mg beads, equivalent to about 100 mg itraconazole. Using the process parameters described above, itraconazole 100 mg hard-gelatin capsules were obtained which met all the requirements, in particular the dissolution specifications. Saperconazole 100 mg hard-gelatin capsules could be obtained by conducting the above-described procedures and using the saperconazole spraying solution.

Claims

1. A bead comprising
 - a) a central, rounded or spherical core;
 - b) a coating film of a hydrophilic polymer and an antifungal agent, and
 - c) a seal-coating polymer layer,characterized in that the core has a diameter from about 600 to about 700 μm (25-30 mesh).
2. A bead according to claim 1 comprising by weight based on the total weight of the bead :
 - a) 20 to 60 percent core material;
 - b) 25 to 50 percent hydrophilic polymer;
 - c) 10 to 25 percent antifungal agent; and
 - d) 2 to 5 percent seal-coating polymer.
3. A bead according to claim 2 wherein the core material is a 25-30 mesh sugar sphere, the hydrophilic polymer is hydroxypropyl methylcellulose and the antifungal agent is itraconazole or saperconazole.
4. A bead according to claim 3 wherein the weight to weight ratio of antifungal agent : hydrophilic polymer is about 1:1 to about 1:2.
5. A bead according to claim 2 wherein the seal-coating polymer is polyethylene glycol.
6. A bead according to claim 2 comprising approximately :
 - a) 26 to 38 percent sugar;
 - b) 32 to 33 percent hydroxypropyl methylcellulose 2910 5 mPa.s.
 - c) 21 to 22 percent itraconazole or saperconazole; and
 - d) 3 to 4 percent polyethylene glycol 20000.
7. A pharmaceutical dosage form comprising an effective antifungal amount of beads as claimed in any one of claims 1 to 6.
8. A dosage form according to claim 7 wherein the dosage form is a hard-gelatin capsule comprising the antifungal agent itraconazole or saperconazole in the form of

beads as claimed in any one of claims 1 to 6.

9. A process for preparing beads as claimed in any one of claims 1 to 6 characterized by,
- 5 a) coating 25-30 mesh cores by spraying with a solution of an antifungal agent and a hydrophilic polymer in an organic solvent consisting of methylene chloride and ethanol in a fluidized-bed granulator equipped with a Wurster (bottom spray) insert;
- 10 b) drying the resulting coated cores in a vacuum tumbler-drier; and
- c) seal-coating the dried cores by spraying with a solution of a seal-coating polymer in an organic solvent consisting of methylene chloride and ethanol in a fluidized-bed granulator equipped with a Wurster (bottom spray) insert.
- 15 10. Drug-coated beads obtainable by a process according to claim 9.

INTERNATIONAL SEARCH REPORT

Inter. Appl. No.

PCT/EP 93/02327

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K9/16 A61K9/50 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 283 992 (JANSSEN) 28 September 1988 see claims 1,6-10 see example 14 ---	1,3,7-10
A	WO,A,89 05634 (SHINETSU) 29 June 1989 see claims see page 6, line 20 - line 23 see page 8, line 20 - line 26 see page 9, line 1 - line 3 see page 10, line 9 - line 11 see page 12, line 7 see page 15, line 16 -----	1,7-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

19 November 1993

Date of mailing of the international search report

19.12.93

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

SCARPONI, U

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 93/02327

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0283992	28-09-88	AU-B- 600107	02-08-90
		AU-A- 1358588	29-09-88
		DE-A- 3874576	22-10-92
		JP-A- 63277674	15-11-88
		SU-A- 1635900	15-03-91
		US-A- 4916134	10-04-90

WO-A-8905634	29-06-89	JP-A- 1165520	29-06-89
		DE-A- 3883227	16-09-93
		EP-A, B 0347461	27-12-89

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☒ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.